UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,517	09/28/2006	Yoshiko Kubo	296115US0PCT	1811

22850 7590 02/24/2011

OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, L.L.P.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
BROWN, COURTNEY A	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
02/24/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/594,517	KUBO ET AL.	
	Examiner	Art Unit	
	COURTNEY BROWN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *9 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-15 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt/Status of Claims

This Office Action is in response to the amendment filed December 17, 2010. Claims 1-20 are pending in the application. Claims 1-8 and 12-17 have been amended. Claims 9 and 16 have been withdrawn as being directed to a non-elected invention. Claims 18-20 are newly added. Claims **1-8, 10-15 and 17-20** are being examined for patentability.

Withdrawn Rejections

Applicant's amendments and arguments filed December 16, 2010 are acknowledged and have been fully considered.

The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application. The objection of the abstract has been **withdrawn** in view of Applicant's amendment.

Maintained Rejections

Applicant's arguments filed December 16, 2010 are acknowledged and have been fully considered.

The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application. The rejection of claims 1-8, 10-15 and 17-20 under 35 U.S.C. 103(a) as being unpatentable over Bosch et al. (US Patent 5,510,118) in view of Yamakawa et al. (*Journal of Controlled Release*, 86(2003) 101-103) **is maintained.**

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8,10-15 and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosch et al. (US Patent 5,510,118) in view of Yamakawa et al. (*Journal of Controlled Release*, 86(2003) 101-103).

Applicant's Invention

Applicant is claiming a process for producing a fine dispersion of a poorly soluble drug, wherein said process comprises : suspending said poorly soluble drug in a liquid containing no deflocculant to obtain a suspension; introducing said suspension into a high-pressure homogenizer to subject the same to high-pressure treatment to obtain a dispersion; and adding a deflocculant to said dispersion to deagglomerate aggregated particles contained therein.

Determination of the scope and the content of the prior art (MPEP 2141.01)

Bosch et al. teach a process of preparing nanoparticulate drug substances comprising the steps of: preparing a premix of the drug substance and a surface modifier, and subjecting the premix to mechanical means to reduce the particle size of the drug substance, the mechanical means producing shear, impact, cavitation and attrition (abstract). Bosch et al. teach that the drug substance must be poorly soluble and dispersible in at least one liquid medium (column 4,lines 56-57) and can selected from a variety of know classes of drugs including anti-arrhythmic, antibiotics, antimycobacterial agents, antiviral agents and astringents (column 5, lines 1-42). Suitable surface modifiers (i.e., deflocculant of instant application) are selected from various polymers, low molecular weight oligomers, natural products and surfactants such as carboxymethylcellulose calcium, hydroxypropylmethylcellulose phthalate , polyvinylpyrrolidone and gum acacia (column 5, line 45 bridging to column 6, lines 1-29). Bosch et al. teach that said particle size refers to a number average particle size of less than about 400 nm wherein at least 90% of the particles have a weight average particle size of less than about 400 nm (column 6, lines 37-54). Bosch et al. teach that the coarse drug substance can be added to a liquid medium to form a premix (column 7, lines 51-53) and then transferred to a mocrofulidizer (high-pressure homogenizer of instant application) and circulated continuously first at a low pressure and then at a maximum capacity of about 3,000 to 30,000 psi until the desired particle size reduction is achieved (column 7, lines 63-67). Bosch et al. teach that it is preferred, **but not essential**, that the surface modifier be present in the premix and the surface modifier and that if not present in the premix, the surface modifier must be added to the

dispersion after attrition. Thereafter, the dispersion can be mixed. Optionally, the dispersion can be subjected to a sonication step (ultrasonic treatment of instant application, limitation of instant claim 20, column 7, lines 55-56 and column 8, lines 16-23 of Bosch et al.).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

The difference between the invention of the instant application and that of Bosch et al. is that Bosch et al. do not expressly teach a process for producing a fine dispersion of 1-cyclopropyl-8-methyl-7-[5-methyl-6- (methylamino)-3-pyridinyl]-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid (i.e., T-3912) . However, it is known in the prior art that T-3192 has low solubility. For example, Yamakaw et al. teach a study evaluating the combined use of polyvinylpyrrodidone and T-3192 in order to obtain a stable liquid formulation of T-3912 (abstract).

Finding of prima facie obviousness

Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Bosch et al. and Yamakaw et al. to devise a process for producing a fine dispersion of 1-cyclopropyl-8-methyl-7-[5-methyl-6-

(methylamino)-3-pyridinyl]-4-oxo- 1,4-dihydro-3-quinolinecarboxylic acid (i.e., T-3912). Yamakaw et al. teach that T-3912 is only sparingly soluble in water: at pHs of 6, 7 and 8, and that its solubility is 1, 1.5 and 8.4 µg/ml, respectively. Taking this into account, in attempting to extend its use in topical application, in particular, for ophthalmic formulations, Yamakaw et al. teaches that the solubility of T-3912 had to be improved. Further, Bosch et al. teach that poorly water soluble drugs tend to have poor bioavailability and be eliminated from the gastrointestinal tract before being absorbed into the circulation (column 1, lines 18-22). One skilled in the art at the time the invention was made would have been motivated to combine the teachings of Bosch et al. and Yamakaw et al. and produce a fine dispersion of T-3912 with the expected benefit of increasing the rate of dissolution of T-3912 by decreasing the particle size (see column 1, lines 25-28 of Bosch et al.) which results in increased bioavailability of T-3912. Therefore, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made because every element of the invention has been fairly suggested by the cited reference.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Examiner's Response to Applicant's Remarks

Applicant's arguments filed on December 16, 2010, with respect to the 103 rejection of claims 1-8,10-15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosch et al. (US Patent 5,510,118) in view of Yamakawa et al. (Journal of Controlled Release, 86(2003) 101-103) have been fully considered but they are not persuasive.

Applicant argues that it has been discovered that the inventive fine dispersions of a poorly soluble drug of Examples 1-15, which were produced by the process of the present invention comprising suspending the poorly soluble drug in a liquid containing no deflocculant to obtain a suspension, introducing the suspension into a high-pressure homogenizer to subject the suspension to a high-pressure treatment to obtain a dispersion, and subsequently adding a deflocculant to the dispersion to deagglomerate aggregated particles contained therein, exhibited superior properties with respect to a narrow particle size distribution and an improved dispersion stability (See e.g., Examples 1-15, Tables 1-8, Figs. 1-7). Applicant further argues that unlike the process of the present invention, Bosch describes that the surface modifier is preferably

present before microfluidization (See e.g., column 7, lines 55-56) and that Bosch mentions that if the surface modifier was not added before microfluidization, then the surface modifier must be added thereafter (See e.g., column 8, lines 16-18) and concludes that a skilled artisan would reasonably expect that fine dispersions of a poorly soluble drug would exhibit either slightly improved properties if the surface modifier is added before microfluidization in accordance with the preferred embodiment described therein, or similar properties regardless of whether the surface modifier is added before or after microfluidization. Applicant argues that contrary to the disclosure of Bosch, Applicants have discovered that fine dispersions of a poorly soluble drug exhibit superior properties with respect to a narrow particle size distribution and an improved dispersion stability when produced by the process of present invention. However, the Examiner disagrees with Applicant's argument because Bosch et al. teach that it is preferred, but not essential, that the surface modifier be present in the premix and the surface modifier and that if not present in the premix, the surface modifier must be added to the dispersion after attrition. Thus, the process step which comprise suspending the poorly soluble drug in a liquid containing no deflocculant to obtain a suspension, introducing the suspension into a high- pressure homogenizer to subject the suspension to a high-pressure treatment to obtain a dispersion, and adding a deflocculant to the dispersion to deagglomerate aggregated particles was *suggested* by Bosch et al. Thus, said this process step would ***intrinsically*** produce fine dispersions of a poorly soluble drug exhibiting superior properties with respect to a narrow particle size distribution and improved dispersion stability.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Courtney A. Brown whose telephone number is 571-270-3284. The examiner can normally be reached on 9:00 am-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Courtney A. Brown
Patent Examiner
Technology Center 1600
Group Art Unit 1617